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Effects of Pulmonary Rehabilitation in Patients with Non-Cystic Fibrosis Bronchiectasis: A Retrospective Analysis of Clinical and Functional Predictors of Efficacy

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Key Words
Bronchiectasis · Pulmonary rehabilitation · Predictors of efficacy

Abstract
Background: International guidelines recommend the inclusion of patients with bronchiectasis in pulmonary rehabilitation (PR) to improve exercise capacity and health-related quality of life (HRQoL). At present, the effect of PR in these patients has been poorly investigated. ***Objective:*** The aim of our retrospective analysis was to evaluate the effects and predictors of success for a PR program in patients with bronchiectasis not related to cystic fibrosis (non-CF bronchiectasis). ***Methods:*** One hundred and thirty-five non-CF bronchiectasis inpatients, allocated to a 3-week PR program, were retrospectively evaluated. Exercise capacity (6-min walk distance, 6MWD), dyspnea (Baseline/Transition Dyspnea Index, BDI/TDI), and HRQoL [EuroQol visual analogue scale (EQ-VAS)] were assessed before and after PR. The relationship between baseline parameters and changes in outcome measures after PR was assessed. Both univariate and multiple logistic analyses were performed to evaluate the presence of independent predictors of the efficacy of PR. ***Results:*** One hundred and eight patients [49 males, mean age 71 years, mean forced expiratory volume in 1 s (FEV_1) 76% predicted] were included. After PR, there was a significant improvement in 6MWD, TDI, and EQ-VAS score ($p < 0.001$). Changes in 6MWD and EQ-VAS score correlated with baseline FEV_1, FEV_1/vital capacity (VC), residual volume, transfer factor of the lung for carbon monoxide, and the number of exacerbations in the previous year. Both univariate and multivariate logistic regression analyses showed that male gender, baseline FEV_1/VC <70%, and >2 exacerbations in the previous year were independent predictors of PR efficacy in terms of an improvement in 6MWD. ***Conclusions:*** Our study supports the inclusion of patients with bronchiectasis in PR programs. Clinical and functional baseline findings partially predict the response to PR in terms of exercise tolerance. Further prospective, randomized, controlled trials are needed.

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Introduction

Bronchiectasis not related to cystic fibrosis (non-CF bronchiectasis) is a persistent or progressive condition characterized by dilated thick-walled bronchi. Patients with non-CF bronchiectasis exhibit persistent or recurrent bronchial infection related to irreversibly damaged bronchi, with symptoms including cough, sputum production, wheeze, dyspnea, and decreased exercise tolerance [1, 2]. Importantly, bronchiectasis is often characterized by airflow obstruction, which can significantly improve after the administration of bronchodilators [3]. Pulmonary function and exercise capacity often deteriorate with time, despite adequate medical interventions, such as antibiotic treatment and bronchodilators [4]. The causes of dyspnea and reduced exercise capacity are multifactorial: altered pulmonary mechanics, inefficient gas exchange, decreased muscle mass, and confounding psychological morbidity lead to a progressive detraining effect [1, 2]. Individuals with non-CF bronchiectasis may also show a health-related quality of life (HRQoL) impairment [5], even at a young age [6].

Pulmonary rehabilitation (PR), a multidisciplinary approach to treat patients with chronic lung diseases, is crucial for the management of chronic obstructive pulmonary disease (COPD) patients [7]. Since PR has traditionally focused on patients with COPD, its effectiveness in other chronic lung diseases has received little attention [8]. The rationale for recommending PR to patients with non-CF bronchiectasis relies primarily on physiological reasoning and on the similarities between this disease and COPD [3, 5]. Moreover, since the pathophysiology of non-CF bronchiectasis involves more factors than only airflow obstruction, PR might represent a useful tool also for patients without airflow obstruction [9]. A dissociation of lung function, dyspnea ratings, and pulmonary extension in bronchiectasis was observed by Martínez-García et al. [10], whereas Lee et al. [11], in an objective assessment of the bronchial tract involved and in a subjective assessment of HRQoL, identified the major determinants of the 6-min walk test (6MWT) in bronchiectasis. These prospective studies on the effect of PR in patients with non-CF bronchiectasis showed short-term improvements in exercise tolerance and HRQoL following a combination of lower limb endurance and strength training (but regardless of inspiratory muscle training) [12] or regular airway clearance therapy [9, 13]. Long-term improvements were observed only for the frequency of acute exacerbations and the time to first exacerbation [9]. Additionally, two retrospective studies demonstrated positive effects in exercise capacity and HRQoL, comparable to those observed in patients with COPD [14], and in pulmonary function, but not in exercise capacity [15]. To date, no study has been specifically planned to assess the predictors of PR efficacy in patients with non-CF bronchiectasis.

Therefore, the aim of this study was to examine the effects of a PR program in patients with non-CF bronchiectasis and to determine whether simple clinical and functional baseline parameters could be considered predictors of a positive effect of a PR program in these patients. Using a large Italian database of inpatients undergoing a 3-week intensive PR program, we retrospectively evaluated the association between baseline characteristics of non-CF bronchiectasis and the outcomes of the PR program.

Methods

Design of the Study

A retrospective analysis was performed on data collected from patients with non-CF bronchiectasis admitted to the IRCCS Rehabilitation Institute of Tradate, Salvatore Maugeri Foundation, from January 2007 to December 2013.

On day 1, patients underwent medical evaluation (medical history and physical examination), pulmonary function tests, and blood gas analysis. On the subsequent day, patients completed Baseline Dyspnea Index (BDI) and EuroQol visual analogue scale (EQ-VAS) measurements and performed the 6MWT. On day 3, patients started the PR program. On the last day before discharge, they underwent the final assessments. The differences between initial and final values were calculated.

Subjects

We examined 135 patients with non-CF bronchiectasis who attended an inpatient PR program. All patients had a primary diagnosis of non-CF bronchiectasis, involving more than one pulmonary lobe, confirmed by high-resolution computed tomography. Age, gender, smoking history, BMI, and the number of exacerbations in the previous year were registered. Patients with a diagnosis of COPD or a smoking history of ≥10 pack-years were excluded. Patients with an acute exacerbation over the previous 4 weeks were excluded, as well as patients who were not able to perform the 6MWT. Patients who did not complete the PR program for intercurrent exacerbations or any unstable medical conditions were also excluded. Contraindications for the participation in the PR program included musculoskeletal disorders, malignant diseases, and unstable cardiac condition.

In all patients, the clinical and functional assessments had been undertaken for clinical reasons at the request of the patient's clinician. The data used in the study are related to the patients who gave their consent to the use of data for research purposes and were analyzed and reported anonymously. No extramural funding was used to support this study.

The study was approved by the Institutional Review Board of the IRCCS Rehabilitation Institute of Tradate, Salvatore Maugeri Foundation, Tradate, Italy.

Pulmonary Function Tests and Arterial Blood Gas Analysis

Vital capacity (VC), forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC), and residual volume (RV) were measured by means of a flow-sensing spirometer and a body plethysmograph connected to a computer for data analysis (Masterlab; Jaeger, Würzburg, Germany). The transfer factor of the lung for carbon monoxide (TLCO) was measured by the single-breath method using a mixture of carbon monoxide and methane (Sensor Medics, Yorba Linda, Calif., USA). VC, FEV_1, TLC, RV, and TLCO were expressed as a percentage of the predicted values, which were obtained from regression equations by Quanjer et al. [16] and Cotes et al. [17]. FEV_1/VC and RV/TLC ratios were taken as indices of airway obstruction and lung hyperinflation, respectively.

Arterial partial pressure of oxygen and arterial partial pressure of carbon dioxide were measured immediately after sampling from a puncture of the radial artery (Gas analyzer ABL 330; Radiometer, Copenhagen, Denmark).

Dyspnea and Health Status

Dyspnea was assessed by the BDI/Transition Dyspnea Index (BDI/TDI) [18]. BDI and TDI are interviewer-administered questionnaires composed of 3 categories (functional impairment, magnitude of task, and magnitude of effort). The BDI allows to quantify the limitation due to dyspnea at baseline, whereas the TDI is useful in determining the change from the baseline level. In the BDI, each category has 5 levels of symptom severity, from 0 to 4, where grade 0 corresponds to the most severe level. The category ratings are then summed to give a score, ranging from 0 to 12, with a lower score indicating a worse clinical condition. The TDI evaluates the change over time in each of the 3 categories. The change from baseline status is rated according to 7 grades, ranging from –3 (major deterioration) to +3 (major improvement), with 0 representing no change. The scores of the 3 categories are then summed to obtain the total score of the TDI, which ranges between –9 (a larger deterioration in dyspnea) and +9. Health status/HRQoL of patients was evaluated by the VAS component of the EQ-5D, reflecting their perceived health state, where 0 indicates the 'worst imaginable health state' and 100 the 'best imaginable health state' [19].

Walking Capacity

Walking capacity was evaluated by means of the distance covered during a 6MWT according to the American Thoracic Society (ATS) statement [20]. The 6MWT was performed by all patients in a 30-meter indoor, level hospital corridor, under the supervision of a physiotherapist, according to the ATS guidelines. All patients received the same instructions before the walk and were encouraged by the physiotherapist who repeated set phrases every minute during the walk. A practice 6MWT was not performed. The 6-min walk distance (6MWD) covered during the test was recorded in meters. Patients were allowed to stop and rest during the test but were instructed to resume walking as soon as they felt able to do so. In all patients, the change in distance covered during 6MWT (Δ6MWD) after PR was recorded. Before and immediately after the 6MWT, patients rated the magnitude of their perceived breathlessness and of their leg fatigue using a modified Borg scale (0–10 points) [21].

PR Program

According to the international recommendations, the PR program was completely tailored to suit the needs of the individual [7]. The program consisted of 15 sessions over a 3-week period. To be included in the study, patients had to perform at least 12 supervised sessions, up to a maximum of 15 sessions. Lower limb endurance training was the main component of the PR program. All patients performed sessions of 30–40 min, using a treadmill or cycle ergometer, depending on the clinically based choice of the physiotherapist and on subject preference. Exercise intensity was based on the initial 6MWT, and patients started their training at 60–70% of the maximum heart rate achieved on the 6MWT. Exercises were then adjusted based on patient tolerance (at least weekly) with the aim of achieving a Borg dyspnea score of 3–5 (moderate to severe). To optimize training load, supplemental oxygen for patients with chronic respiratory failure and interval training for very compromised patients were adopted. Each session also included supervised upper limb training; patients used an arm ergometer or performed calisthenic exercises holding a light weight. In relation to the patients' needs, the PR program could also include other components, such as airway clearance techniques, pursed lip breathing, and exhalation on effort as well as forward-lean position to improve diaphragm activity and to optimize the recruitment of accessory muscles of respiration, and inspiratory muscle training using threshold loading devices. Finally, each patient participated in educational activities, individually (at least 2 times) and in groups (at least 3 times), regarding self-management, airway clearance techniques, adherence to therapy, and nutritional support. The total daily duration of activities was 2–3 h, and the entire program was conducted in the hospital.

Statistical Analysis

The design of the study was retrospective. Continuous data are reported as the mean ± standard deviation (SD), unless otherwise specified. The distribution of variables was assessed by means of the Kolmogorov-Smirnov goodness-of-fit test. Relationships between variables were assessed by Pearson's correlation coefficient (r), and Spearman's rank correlation coefficient (r_s), if appropriate. Comparisons between quantitative and qualitative variables were determined by paired and unpaired t tests, and the χ^2 test, if appropriate.

To evaluate the role of baseline characteristics in predicting PR efficacy, we divided the subjects into different subgroups according to (a) gender, (b) airflow obstruction (FEV_1/VC ≥70%, n = 48; FEV_1/VC <70%, n = 60), (c) pulmonary hyperinflation (RV ≤120% pred., n = 45; RV >120% pred., n = 63), and (d) the number of exacerbations during the previous year (≤2, n = 76; >2, n = 32).

Both univariate and multivariate logistic analyses were performed to evaluate the presence of independent predictors of efficacy of PR, which was expressed by a significant increase in 6MWD (≥30 m) [22], by a significant increase in TDI (≥1 point) [23], or by a significant increase in EQ-VAS score (≥8 points) [24].

Correlations between baseline variables and changes after PR in 6MWD, dyspnea, and HRQoL were also analyzed. Finally, the influence on the presence of airflow obstruction, gender, and exacerbations in the previous year was investigated.

Data analyses and graphical presentations were performed using GraphPad Prism 5 (GraphPad Software, San Diego, Calif., USA) and SPSS version 20 (IBM, Armonk, N.Y., USA). A p value <0.05 was considered statistically significant.

Table 1. Baseline characteristics of all study patients and of the 2 subgroups of patients categorized according to the presence of airflow obstruction

	All patients (n = 108)	Patients with airflow obstruction (n = 60)	Patients without airflow obstruction (n = 48)	p value[1]
Age, years	71±13	72±13	70±13	0.447
Females	59 (55%)	33 (55%)	26 (54%)	0.932
Current or ex-smoker	31 (29%)	18 (30%)	13 (27%)	0.905
FEV_1, % pred.	76±27	63±23	93±21	<0.001
VC, % pred.	88±21	83±21	94±20	0.006
FEV_1/VC, %	66±14	56±12	78±5	<0.001
RV, % pred.	135±43	145±45	121±37	0.003
TLC, % pred.	103±21	106±22	101±19	0.227
RV/TLC, %	54±15	57±9	49±19	0.006
TLCO, % pred.	68±21	63±20	75±21	0.011
BMI	26±5	25±4	27±5	0.017
PaO_2, mm Hg	76±8	74±7	79±9	0.006
$PaCO_2$, mm Hg	38±5	38±6	37±3	0.204
Exacerbations in the previous year	2±1	2.4±1.2	1.6±0.7	<0.001

Values are expressed as the mean ± SD unless indicated otherwise. PaO_2 = Arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide. Comparisons between variables were determined by the unpaired t test and the χ^2 test. [1] Patients with airflow obstruction versus patients without airflow obstruction.

Results

A total of 108 patients were considered eligible for the study. Sixty patients (56%) were receiving regular inhaled pharmacologic treatment (bronchodilators and corticosteroids) in relation to the presence of airflow obstruction. Twelve patients (11%) were under long-term oxygen therapy, 8 of them with airflow obstruction, and 32 patients (30%) have had >2 exacerbations in the previous year, 21 of them with airflow obstruction.

The characteristics of the patients with non-CF bronchiectasis are reported in table 1. As compared to patients without airflow obstruction, patients with airflow obstruction showed a worse exercise capacity and quality of life (6MWD before PR, p = 0.023, and EQ-VAS score before PR, p = 0.011, respectively; table 2).

After PR, a significant improvement in 6MWD, EQ-VAS score, and TDI was found in all patients (table 2). The 6MWD improved by 35 ± 43 m (p < 0.0001). Dyspnea showed a clinically significant reduction from the BDI, corresponding to a change of ≥1 unit in 90%. The EQ-VAS score improved by 15 ± 12 (p < 0.0001). As compared to patients without airflow obstruction, patients with airflow obstruction showed a higher improvement in 6MWD and EQ-VAS score (p = 0.046 and p = 0.038, respectively). No differences were observed in BDI and TDI between the 2 groups (table 2).

With regard to other potential predictors of PR efficacy, male patients showed a higher improvement in 6MWD and EQ-VAS score after PR (p = 0.006 and p = 0.043, respectively), whereas patients with >2 exacerbations in the previous year showed a higher improvement in 6MWD after PR (p = 0.019).

Percentages of patients with non-CF bronchiectasis and with a significant change in 6MWD (≥30 m) after PR, in relation to the presence of the independent predictors considered, are showed in figure 1 (χ^2 test for trend: 17.40; p < 0.0001).

Improvement in 6MWD and in EQ-VAS score was directly correlated with baseline hyperinflation (r_s = 0.26; p = 0.007) and the number of exacerbations in the previous year (r_s = 0.25; p = 0.008) and negatively with airflow obstruction (r_s = –0.27; p = 0.005). Moreover, a change in EQ-VAS score was also negatively correlated with TLCO (r_s = –0.32; p = 0.003; table 3).

Tables 4 and 5 show the results of the univariate and multivariate analyses, taking as dependent variables a clinically significant improvement in 6MWD, EQ-VAS score, and TDI, and as independent variables the baseline characteristics used for the defined subgroups. Both univariate and multivariate analyses show that the change in 6MWD was significantly associated with male gender, baseline FEV_1/VC (subjects with FEV_1/VC <70% had a greater improvement), and number of exacerbations in

Table 2. Outcome measures of PR in all study patients and in the 2 subgroups of patients categorized according to the presence of airflow obstruction

	All patients (n = 108)	Patients with airflow obstruction (n = 60)	Patients without airflow obstruction (n = 48)	p value[1]
EQ-VAS score before PR	60±17	56±18	65±15	0.011
EQ-VAS score after PR	75±13	74±14	77±12	0.157
ΔEQ-VAS score	15±12	17±13	12±10	0.038
6MWD before PR	443±107	423±121	470±82	0.023
6MWD after PR	479±107	465±117	496±91	0.141
Δ6MWD	35±43	43±49	26±30	0.046
BDI	7.3±2.9	7±3.3	7.7±2.3	0.261
TDI	4±2.6	3.9±2.7	4.2±2.4	0.467
Borg dyspnea before PR	3.7±2.1	4.3±2.0	3±1.9	0.002
Borg dyspnea after PR	2.8±1.9	3±2.1	2.6±1.7	0.248
ΔBorg dyspnea	0.8±1.8	1.2±2	0.4±1.3	0.022
Borg fatigue before PR	3.5±2	3.8±2	3.2±2	0.164
Borg fatigue after PR	2.7±1.7	2.8±1.9	2.6±1.5	0.508
ΔBorg fatigue	0.9±1.9	1±1.9	0.7±2	0.452

Values are expressed as the mean ± SD. Δ = Change after PR in outcome measures. Comparisons between variables were determined by the unpaired t test. [1] Patients with airflow obstruction versus patients without airflow obstruction.

the previous year (subjects with >2 exacerbations showed a greater improvement). Male gender was also significantly associated with a change in EQ-VAS score, both in univariate and multivariate analyses.

Discussion

In this retrospective study, we examined the role of clinical and functional parameters at baseline in determining benefits after a 3-week PR program in 108 subjects with non-CF bronchiectasis. All patients showed an improvement in PR outcomes. Of interest, 3 independent factors, male gender, airflow obstruction (FEV_1/VC <70%), and frequent exacerbations in the previous year, were identified to be associated with clinically significant improvement in 6MWD and EQ-VAS score.

The effect of PR in patients with non-CF bronchiectasis has not yet been extensively investigated. Newall et al. [12] conducted the first study to assess the effects of exercise training in patients with bronchiectasis; this prospective study showed that an 8-week PR program was effective in improving the exercise capacity and health status, regardless of the addition of inspiratory muscle training [13]. In addition, two other prospective studies, based on an 8-week PR program for patients with non-CF bronchiectasis, have recently been performed [9, 13]. Mandal et al. [13] found that PR in addition to regular chest physiotherapy led to significant improvement in exercise capacity and HRQoL, as compared to patients practicing regular chest physiotherapy alone. Moreover, these results were maintained at 12 weeks after the end of PR. Similarly to Mandal et al. [13], Lee et al. [9] observed short-term improvement in PR outcomes, with a reduction in

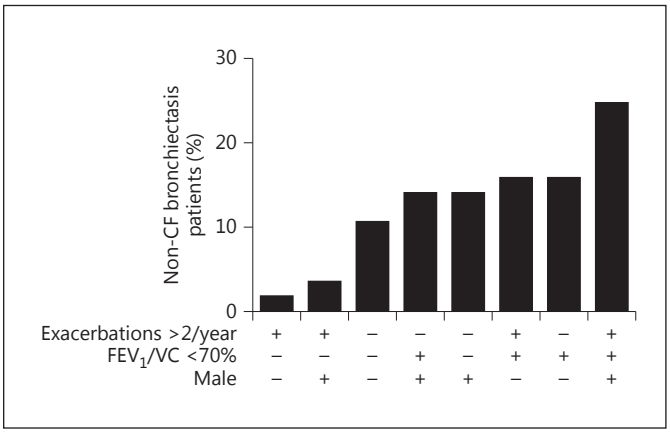

Fig. 1. Percentage of patients with non-CF bronchiectasis and significant change in 6MWD (≥30 m) after PR, in relation to the presence of the independent predictors considered (χ^2 test for trend: 17.40; $p < 0.0001$).

Table 3. Relationship between baseline variables and the change in the 3 outcomes Δ6MWD, ΔEQ-VAS score, and TDI after the PR program in all study patients

	Δ6MWD	ΔEQ-VAS score	TDI
BMI	n.s.	n.s.	n.s.
FEV_1 (% pred.)	$r_s = -0.26$; $p = 0.007$	$r_s = -0.37$; $p < 0.0001$	n.s.
VC (% pred.)	$r_s = -0.19$; $p = 0.05$	$r_s = -0.35$; $p = 0.0002$	n.s.
FEV_1/VC	$r_s = -0.27$; $p = 0.005$	$r_s = -0.27$; $p = 0.005$	n.s.
RV (% pred.)	$r_s = 0.26$; $p = 0.007$	$r_s = 0.22$; $p = 0.02$	n.s.
TLC (% pred.)	n.s.	n.s.	n.s.
RV/TLC	n.s.	$r_s = 0.23$; $p = 0.02$	n.s.
TLCO (% pred.)	n.s.	$r_s = -0.32$; $p = 0.003$	n.s.
PaO_2 (mm Hg)	n.s.	n.s.	n.s.
$PaCO_2$ (mm Hg)	n.s.	n.s.	n.s.
Exacerbations in the previous year	$r_s = 0.25$; $p = 0.008$	$r_s = 0.26$; $p = 0.006$	n.s.

Δ = Change after PR in outcome measures; n.s. = nonsignificant correlation; PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide.

Table 4. Results of the univariate logistic regression analysis

	6MWD		EQ-VAS score		TDI	
	OR	95% CI	OR	95% CI	OR	95% CI
Male	2.56*	1.17–5.60	2.83***	1.12–7.15	1.18	0.35–4.00
FEV_1/VC <70%	6**	2.78–12.93	1.24	0.53–2.90	1.94	0.56–6.74
RV >120%	1.08	0.49–2.37	1.45	0.61–3.40	0.86	0.26–2.82
Exacerbations >2	6.29**	2.32–17.08	1.88	0.68–5.18	2.54	0.53–12.17

OR = Odds ratio; CI = confidence interval. An increase of >29 m in the 6MWT, an increase of >7 points in EQ-VAS, and an increase in TDI (≥1 point) were adopted as dependent variables. Male gender, the presence of functional abnormalities (FEV_1/VC <70% or RV >120% pred.), and frequent exacerbations in the previous year (>2) were taken as independent variables. * $p = 0.017$; ** $p < 0.001$; *** $p = 0.024$.

Table 5. Results of the multivariate logistic regression analysis

	6MWD		EQ-VAS score		TDI	
	OR	95% CI	OR	95% CI	OR	95% CI
Male	2.74*	1.09–6.86	2.90****	1.09–7.70	1.08	0.31–3.72
FEV_1/VC <70%	2.69**	1.05–6.97	1.04	0.40–2.71	0.37	0.10–1.36
RV >120%	2.42	0.98–5.99	1.68	0.67–4.22	0.91	0.26–3.16
Exacerbations >2	3.52***	1.17–10.54	1.33	0.42–4.16	3.68	0.69–19.7

OR = Odds ratio; CI = confidence interval. An increase of >29 m in the 6MWT, an increase of >7 points in EQ-VAS, and an increase in TDI (≥1 point) were adopted as dependent variables. Male gender, the presence of functional abnormalities (FEV_1/VC <70% or RV >120% pred.), and frequent exacerbations in the previous year (>2) were taken as independent variables. * $p = 0.031$; ** $p = 0.039$; *** $p = 0.025$; **** $p = 0.032$.

the frequency of exacerbations over 12 months. Our study included patients with a similar airflow obstruction degree, who also experienced significant improvements in exercise capacity and health status. The mean improvement in the 6MWT of our study (35 m for all subjects and 43 m for subjects with airflow obstruction) is consistent with that (41 m) given in the study of Lee et al. [9] and with those of the previous retrospective studies (53 and 25 m, respectively) [14, 15]. Of interest, the extent of improvement in 6MWD is similar to the minimal clinically important difference in COPD [22]. Even if the clinical significance of the improvement in exercise capacity requires confirmation in non-CF bronchiectasis, these findings suggest that exercise capacity improvement in non-CF bronchiectasis can be achieved using training principles similar to those applied in COPD [7, 8].

In our study, a significant improvement in HRQoL was found after PR. We adopted the VAS component of the EQ-5D, a simple instrument which has been demonstrated to be responsive to PR in COPD patients [24, 25]. In this regard, given the variety of instruments used for the measurement of quality of life, a comparison with previous studies is not easy to perform: St. George's Respiratory Questionnaire [12, 13], Chronic Respiratory Disease Questionnaire [9, 14], and parameters without rating [15]. Notably, the magnitude of improvement in the EQ-VAS score observed in our study is similar to that obtained from a large cohort of patients with COPD, exceeding the minimal clinically important difference proposed for COPD [24]. However, this finding has not yet been defined for non-CF bronchiectasis and needs further study.

The duration of the PR program might impact the effects of exercise capacity in patients with non-CF bronchiectasis. As compared to the majority of the previous studies on the effects of PR in patients with non-CF bronchiectasis, in our study, we adopted a shorter PR program. Notably, 3 out of the 5 previous studies on bronchiectasis were conducted with a longer PR than ours, and the remaining 2 studies had a similar duration [9, 14]. Although the ATS/ERS statement of pulmonary rehabilitation suggests a minimum of 20 sessions as a practice guideline [26], the same statement, and its update [7], reports that there is no consensus on the optimal duration of PR. The ATS/ERS statement of 2013 also argues that the duration of PR can be influenced by the resources of the program and reimbursement issues. It is worth noting that there is evidence that in COPD patients, a PR of the same duration as ours was effective on exercise capacity and quality of life [27–30].

In the present study, we provided the first evidence that patients with a more severe disease, both in terms of airflow obstruction and hyperinflation and the number of exacerbations in the previous year, showed a higher magnitude of improvement in 6MWD and EQ-VAS score after PR, as compared to other patients. Similar evidence has been reported in patients with COPD [24, 31, 32]. As well as for patients with COPD, it is conceivable that even patients with non-CF bronchiectasis and a poor baseline lung function are at risk of entering a downward spiral of dyspnea, sedentariness, demotivation, and, finally, deconditioning [33]. As a consequence, these deconditioned and demotivated patients may have a larger capacity for improvement than patients with a more preserved lung function and exercise capacity, and, thus, they may show larger improvement after exercise training.

To date, data in the literature on the factors predictive of PR in patients with bronchiectasis are very scant. In a previous study by van Zeller et al. [15], determining the potential influence of clinical and functional baseline parameters on PR outcomes in 41 patients with bronchiectasis, pulmonary function, arterial blood gases and 6MWD were measured before and after PR. No interaction between PR outcomes and gender, bacterial colonization, or exacerbations was found [15]. In our study, changes in 6MWD and EQ-VAS score, but not in TDI, were determined by some baseline findings, i.e. male gender, the presence of airflow obstruction, and a higher number of exacerbations in the previous year. Thus, it is a subject of debate whether these findings can suggest real pathophysiological differences in the response to PR in these subgroups of patients with non-CF bronchiectasis. The differences in results may be due, at least in part, to differences in patient selection, outcome measures, interventions, and the statistical methods used. Notably, we included 108 patients, compared to 41 examined in the study of van Zeller et al. [15], with a much wider range in terms of FEV_1/VC and FEV_1. Furthermore, there is some evidence of lower improvements in HRQoL after PR in women, as compared to men, with COPD [34], although the impact of gender-related differences in PR outcomes remains to be defined [35].

Despite reporting original findings with a potential clinical significance, this study has some limitations. Firstly, the retrospective design might limit the validity of the results observed. Similarly, the absence of a control group and the lack of control for the assessment of concurrent etiological conditions and comorbidities might also limit the importance of our findings. Furthermore, in this study, we could not consistently collect any data

concerning the bacterial colonization of the bronchiectasis. Interestingly, the only 2 [13, 15] of the 5 studies mentioned above which reported data on colonization did not find any differences between patients with and those without colonization in terms of PR effects. Finally, as indicated above, the validity of a clinically significant change in 6MWD and EQ-VAS score already demonstrated in COPD still needs to be established in patients with non-CF bronchiectasis. Given these limitations, further prospective, randomized, and controlled studies are needed.

In conclusion, our results, even if of an exploratory character and not generalizable because of the single-center nature of the study, clearly indicate that a PR program, in which the principles of exercise prescription were derived from COPD, is a valid approach also for patients with non-CF bronchiectasis. In addition, in our patients, clinical and functional baseline features were able to partially predict the response to PR in terms of exercise tolerance. Our findings also suggest that patients with non-CF bronchiectasis and severe pulmonary impairment should be included in rehabilitation programs, since they may achieve relevant results.

Disclosure Statement

All authors declare that they did not have any relationship with the industry in the past 2 years.

References

1 McShane PJ, Naureckas ET, Tino G, Strek ME: Non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2013;188:647–656.
2 Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis (Non-CF) Guideline Group: British Thoracic Society guideline for non-CF bronchiectasis. Thorax 2010;65:i1–i58.
3 Martínez-García MA, Soler-Cataluña JJ, Perpiñá-Tordera M, Román-Sánchez P, Soriano J: Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest 2007;132:1565–1572.
4 Ten Hacket NH, Wijstra PJ, Kerstjens HA: Treatment of bronchiectasis in adults. BMJ 2007;335:1089–1093.
5 Martínez-García MA, Perpiñà-Tordera M, Román-Sánchez P, Soler-Cataluña JJ: Quality-of-life determinants in patients with clinically stable bronchiectasis. Chest 2005;128:739–745.
6 Gokdemir Y, Hamzah A, Erdem E, Cimsit C, Ersu R, Karakoc F, Karadag B: Quality of life in children with non-cystic-fibrosis bronchiectasis. Respiration 2014;88:46–51.
7 Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al; ATS/ERS Task Force on Pulmonary Rehabilitation: An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188:e13–e64.
8 Holland AE, Wadell K, Spruit MA: How to adapt the pulmonary rehabilitation programme to patients with chronic respiratory disease other than COPD. Eur Respir Rev 2013;22:577–586.
9 Lee AL, Hill CJ, Cecins N, Jenkins S, McDonald CF, Burge AT, Rautela L, Stirling RG, Thompson PJ, Holland AE: The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis – a randomised controlled trial. Respir Res 2014,15:44.
10 Martínez-García MA, Perpiñá-Tordera M, Soler-Cataluña JJ, Román-Sánchez P, Lloris-Bayo A, González-Molina A: Dissociation of lung function, dyspnea ratings and pulmonary extension in bronchiectasis. Respir Med 2007;101:2248–2253.
11 Lee AL, Button BM, Ellis S, Stirling R, Wilson JW, Holland AE, Denehy L: Clinical determinants of the 6-minute walk test in bronchiectasis. Respir Med 2009;101:2248–2253.
12 Newall C, Stockley RA, Hill SL: Exercise training and inspiratory muscle training in patients with bronchiectasis. Thorax 2005;60:943–948.
13 Mandal P, Sidhu MK, Kope L, Pollock W, Stevenson LM, Pentland JL, Turnbull K, Mac Quarrie S, Hill AT: A pilot study of pulmonary rehabilitation and chest physiotherapy versus chest physiotherapy alone in bronchiectasis. Respir Med 2012;106:1647–1654.
14 Ong HK, Lee AL, Hill CJ, Holland AE, Denehy L: Effects of pulmonary rehabilitation in bronchiectasis: a retrospective study. Chron Respir Dis 2011;8:21–30.
15 van Zeller M, Mota PC, Amorim A, Viana P, Martins P, Gaspar L, Hespanhol V, Gomes I: Pulmonary rehabilitation in patients with bronchiectasis: pulmonary function, arterial blood gases, and the 6-minute walk test. J Cardiopulm Rehabil Prev 2012;32:278–283.
16 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC: Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5–40.
17 Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC: Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:41–52.
18 Mahler DA, Guyatt GH, Jones PW: Clinical measurements of dyspnoea; in Mahler DA (ed): Dyspnea. New York, Marcel Dekker, 1998, pp 149–198.
19 Brooks R, Rabin R, De Charro F: The Measurement and Validation of Health Status Using EQ-5D: A European Perspective; Evidence from the EuroQol BIOMED Research Programme, ed 1. Dordrecht, Kluwer Academic Publishers, 2003.
20 ATS statement: guidelines for the six-minute walk test. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. Am J Respir Crit Care Med 2002;166:111–117.
21 Mahler DA, Horowitz MB: Perception of breathlessness during exercise in patients with respiratory disease. Med Sci Sports Exerc 1994;26:1078–1081.
22 Polkey MI, Spruit MA, Edwards LD, Watkins ML, Pinto-Plata V, Vestbo J, Calverley PMA, Tal-Singer R, Agusti A, Bakke PS, Coxson HO, Lomas DA, MacNee W, Rennard S, Silverman EK, Miller BE, Crim C, Yates J, Wouters EFM, Celli B: Six-minute-walk test in chronic obstructive pulmonary diseases: minimal clinically important difference for death or hospitalization. Am J Respir Crit Care Med 2013;187:382–386.
23 Witek TJ Jr, Mahler DA: Minimal important difference of the transition dyspnoea index in a multinational clinical trial. Eur Respir J 2003;21:267–272.
24 Zanini A, Aiello M, Adamo D, Casale S, Cherubino F, Della Patrona S, Raimondi E, Zampogna E, Chetta A, Spanevello A: Estimation of minimal clinically important difference in EQ-VAS score after pulmonary rehabilitation in patients with COPD. Respir Care 2015;60:88–95.

25 Ringbaek T, Brøndum E, Martínez G, Lange P: EuroQol in assessment of the effect of pulmonary rehabilitation COPD patients. Respir Med 2008;102:1563–1567.
26 Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, Garvey C, Goldstein R, Gosselink R, Lareau S, MacIntyre N, Maltais F, Morgan M, O'Donnell D, Prefault C, Reardon J, Rochester C, Schols A, Singh S, Troosters T; ATS/ERS Pulmonary Rehabilitation Writing Committee: American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006;173:1490–1513.
27 Fuchs-Climent D, Le Gallais D, Varray A, Desplan J, Cadopi M, Préfaut C: Quality of life and exercise tolerance in chronic obstructive pulmonary disease: effects of a short and intensive inpatient rehabilitation program. Am J Phys Med Rehabil 1999;78:330–335.
28 Clini E, Foglio K, Bianchi L, Porta R, Vitacca M, Ambrosino N: In-hospital short-term training program for patients with chronic airway obstruction. Chest 2001;120:1500–1505.
29 Cilione C, Lorenzi C, Dell Orso D, Garuti G, Rossi G, Totaro L, Clini E: Predictors of change in exercise capacity after comprehensive COPD inpatient rehabilitation. Med Sci Monit 2002;8:CR740–CR745.
30 Carone M, Patessio A, Ambrosino N, Baiardi P, Balbi B, Balzano G, et al: Efficacy of pulmonary rehabilitation in chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD): the Maugeri Study. Respir Med 2007;101:2447–2453.
31 Altenburg WA, de Greef MHG, ten Hacken NHT, Wempe JB: A better response in exercise capacity after pulmonary rehabilitation in more severe COPD patients. Respir Med 2012;106:694–700.
32 Zanini A, Chetta A, Gumiero F, Della Patrona S, Casale S, Zampogna E, et al: Six-minute walking distance improvement after pulmonary rehabilitation is associated with baseline lung function in clinically complex COPD patients. A retrospective study. Biomed Res Int 2013;2013:483162.
33 MacIntyre NR: Mechanisms of functional loss in patients with chronic lung disease. Respir Care 2008;53:1177–1184.
34 Foy CG, Rejeski WJ, Berry MJ, Zaccaro D, Woodard CM: Gender moderates the effects of exercise therapy on health-related quality of life among COPD patients. Chest 2001;119:70–76.
35 Robles PG, Brooks D, Goldstein R, Salbach N, Mathur S: Gender-associated differences in pulmonary rehabilitation outcomes in people with chronic obstructive pulmonary disease. J Cardiopulm Rehabil Prev 2014;34:87–97.